

**Clinical trial results:****A Randomized Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed after Therapy with CHOP-R or an Equivalent Regimen and are Ineligible for Stem Cell Transplant****Summary**

EudraCT number	2012-001790-86
Trial protocol	GB ES DE FR HU IT CZ DK BG PL BE AT SK RO
Global end of trial date	14 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 August 2019
First version publication date	04 August 2019

Trial information**Trial identification**

Sponsor protocol code	PIX306
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01321541
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CTI BioPharma Corp
Sponsor organisation address	3101 Western Avenue, Suite 800, Seattle, United States, 98121
Public contact	Ekaterina Efremova, PSI Company Ltd., , +7 812320 3855 0032, Ekaterina.Efremova@psi-cro.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2018
Global end of trial reached?	Yes
Global end of trial date	14 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy (as measured by progression-free survival [PFS]) of pixantrone + rituximab compared with gemcitabine + rituximab in patients with a diagnosis of de novo diffuse large B-cell lymphoma (DLBCL), DLBCL transformed from indolent lymphoma, or follicular lymphoma (FL) Grade 3 who had relapsed after at least 1 prior chemotherapy regimen and who were currently ineligible for high-dose (myeloablative) chemotherapy and stem cell transplant (SCT).

Sample size was based on the estimation that 195 PFS events (adjudicated by the Independent Radiology Committee [IRC]) were required to detect at least a 35% improvement (i.e., HR = 0.65) in PFS with 85% power and a 2-sided alpha of 0.05 (Amendments 8 & 9). For the secondary endpoint of overall survival (OS), it was planned to continue the study until 220 deaths had occurred (that required several months of follow-up after the core database lock for primary endpoint and first interim analysis of OS).

Protection of trial subjects:

Patients were to give freely their written informed consent before their selection in the study. Informed consent to collect information on patient's survival status was obtained from subjects at the time of enrolment.

Patients were provided with updated information and re-consented if substantial changes in the study occurred due to study protocol amendments or new information about the study drug became available.

This study was performed in accordance with Good Clinical Practice standards.

Patient safety was monitored by an Independent Data Monitoring Committee (IDMC) whose responsibilities included: 1) minimization of the patients' exposure to an unsafe therapy or dose, 2) evaluation of the toxicity and appropriateness of doses in both arms in order to make recommendations for changes in study, if appropriate, 3) advising on the need for dose adjustments because of safety issues, 4) any other safety associated assessments, including endorsing continuation of the study per protocol, and 5) providing the interim OS analyses and release of the unblinded OS results to the sponsor after all patients had completed study treatment.

Background therapy:

Rituximab was administered in combination with both the investigational drug (pixantrone) and comparator drug (gemcitabine). Combining pixantrone chemotherapy with the anti-CD20 agent rituximab was expected to produce synergistic effects with minimal overlapping toxicity and minimal drug interactions.

Evidence for comparator:

The choice of comparator (gemcitabine) was based on the National Comprehensive Cancer Network (NCCN) guidelines published at that time, for patients with relapsed or refractory DLBCL who are not candidates for SCT, recommending entry to a clinical study, or single-agent, doublet, or multiagent regimens, some containing gemcitabine and/or rituximab. The European Society of Medical Oncology (ESMO) guidelines also propose a gemcitabine-based regimen including rituximab as salvage treatment, or clinical trials with novel drugs, in patients non-eligible for transplant. Small studies have shown promising results in patients with relapsed or refractory DLBCL. The combination of gemcitabine and rituximab therefore appeared to be a reasonable therapeutic option in patients with relapsed non-Hodgkin lymphoma (NHL) if ineligible for SCT.

Actual start date of recruitment	01 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 102
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Czech Republic: 28
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 31
Worldwide total number of subjects	312
EEA total number of subjects	183

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	66
From 65 to 84 years	233
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

The first patient, first visit was on 20 April 2011. The study was closed for enrolment in August 2017 when 312 patients had been randomized. Patients were randomized in North America (2 countries) and Europe (16 countries).

Pre-assignment

Screening details:

438 screened; 126 screen failures due to: inclusion/exclusion criteria not met (108), inclusion/exclusion criteria not met and other (4), consent withdrawn (4), inclusion/exclusion criteria not met and consent withdrawn (3), consent withdrawn and other (1), and other (6)

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Blinding implementation details:

Treatment assignment was known to investigators, site personnel, and patients, but the sponsor (except certain sponsor personnel responsible for pharmacovigilance activities, regulatory submissions and GCP Compliance) and the IRC remained blinded during the study until core database lock. At the time of core database lock, the sponsor was unblinded to all data except the OS datasets. Deaths contributing to PFS events in the core locked database were part of the unblinded data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pixantrone + Rituximab

Arm description:

Investigational therapy arm: The intent-to-treat (ITT) population included all 155 patients randomized to pixantrone + rituximab (pixantrone + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (153 patients); 2 patients were excluded from the safety population. The safety population was used for all safety analyses.

83 patients in the ITT population discontinued treatment due to: progressive disease (47), adverse event (21), consent withdrawal (6), death (5), or other reason (4).

Arm type	Experimental
Investigational medicinal product name	Pixantrone + Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pixantrone was supplied as a powder in a vial containing 50 mg pixantrone dimaleate equivalent to 29 mg pixantrone. Reconstitution to a solution containing pixantrone 5.8 mg/mL was done by adding 5 mL sterile 0.9% Sodium Chloride for Injection. Pixantrone was given in up to six 28-day cycles, consisting of pixantrone 50 mg/m² (in its base form) IV on Days 1, 8, and 15 of each cycle.

Rituximab was a sterile, clear, colorless, preservative-free, liquid concentrate for IV administration. Rituximab was supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The necessary amount of rituximab was withdrawn and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in water. Rituximab was given in up to six 28-day cycles at a dose of 375 mg/m² IV on Day 1 of each cycle.

Rituximab was administered prior to pixantrone when both drugs were given on Day 1 of each cycle.

Arm title	Gemcitabine + Rituximab
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Arm description:

Control therapy arm: The intent-to-treat (ITT) population included all 157 patients randomized to gemcitabine + rituximab (gemcitabine + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (149 patients); 8 patients were excluded from the safety population. The safety population was used for all safety analyses.

96 patients discontinued treatment due to: progressive disease (50), adverse event (15), consent withdrawal (16), death (10), or other reason (5).

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine + Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was supplied as a lyophilized powder in vials containing 200 mg or 1 g gemcitabine. The powder was reconstituted to a solution containing gemcitabine 38 mg/mL by adding 5 mL or 25 mL of sterile 0.9% Sodium Chloride Injection without preservatives. Gemcitabine 1000 mg/m² was given IV in up to six 28-day cycles on Days 1, 8, and 15 of each cycle.

Rituximab was a sterile, clear, colorless, preservative-free, liquid concentrate for IV administration. Rituximab was supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The necessary amount of rituximab was withdrawn and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in water. Rituximab was given in up to six 28-day cycles at a dose of 375 mg/m² IV on Day 1 of each cycle.

Rituximab was administered prior to gemcitabine when both drugs were given on Day 1 of each cycle.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Treatment assignment was known to investigators, site personnel, and patients, but the sponsor (except certain sponsor personnel responsible for pharmacovigilance activities, regulatory submissions and GCP Compliance) and the Independent Radiology Committee (IRC) remained blinded during the study until core database lock.

Number of subjects in period 1	Pixantrone + Rituximab	Gemcitabine + Rituximab
Started	155	157
Completed treatment	72	61 ^[2]
Completed	52	63
Not completed	103	94
Adverse event, serious fatal	94	84
Consent withdrawn by subject	6	8
Physician decision	1	-
Lost to follow-up	1	2
Site closed; lack of compliance	1	-

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the study is greater than the number who completed treatment because patients who discontinued treatment entered the Follow-up periods (Early, Intermediate, and/or Survival) to be followed for safety and progression and/or survival. The number of patients who completed the study consists of patients who completed treatment and completed the study (i.e., the Follow-up period[s]) plus patients who discontinued treatment and completed the study.

Baseline characteristics

Reporting groups

Reporting group title	Pixantrone + Rituximab
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Reporting group description:

Investigational therapy arm: The intent-to-treat (ITT) population included all 155 patients randomized to pixantrone + rituximab (pixantrone + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (153 patients); 2 patients were excluded from the safety population. The safety population was used for all safety analyses.

83 patients in the ITT population discontinued treatment due to: progressive disease (47), adverse event (21), consent withdrawal (6), death (5), or other reason (4).

Reporting group title	Gemcitabine + Rituximab
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Reporting group description:

Control therapy arm: The intent-to-treat (ITT) population included all 157 patients randomized to gemcitabine + rituximab (gemcitabine + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (149 patients); 8 patients were excluded from the safety population. The safety population was used for all safety analyses.

96 patients discontinued treatment due to: progressive disease (50), adverse event (15), consent withdrawal (16), death (10), or other reason (5).

Reporting group values	Pixantrone + Rituximab	Gemcitabine + Rituximab	Total
Number of subjects	155	157	312
Age categorical			
At baseline, most patients were 65 years old or older (78.8% overall). The median age of patients was 73.0 years ranging from 26 to 91 years. Age was well balanced between the treatment groups (p = 0.535).			
Units: Subjects			
Adults (18-64 years)	36	30	66
From 65-84 years	113	120	233
85 years and over	6	7	13
Age continuous			
Units: years			
median	73	73	
full range (min-max)	30 to 91	26 to 90	-
Gender categorical			
At baseline, just over half of the patients were women (56.4%). Gender was well balanced between the treatment groups (p = 0.819).			
Units: Subjects			
Female	86	90	176
Male	69	67	136
Region			
Two thirds of patients (66.7%) were enrolled in Europe and one third (33.3%) in North America. Region was well balanced between the treatment groups.			
Units: Subjects			
North America	51	53	104
Europe	104	104	208
Race			
The large majority (96.8%) of patients were white. Race was well balanced between the treatment groups (p = 0.165).			
Units: Subjects			

White	147	155	302
Black or African American	4	1	5
Asian	1	1	2
Other	2	0	2
Unknown	1	0	1
Histological subtype assessed by local investigators			
The most common histological subtype assessed by local investigators was DLBCL (77.6% of patients), 13.8% of patients had DLBCL transformed from indolent, and 8.7% had follicular lymphoma (FL) Grade 3 lymphoma. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.644).			
Units: Subjects			
DLBCL	122	120	242
DLBCL transformed from indolent	22	21	43
FL Grade 3	11	16	27
Histology assessed by CPRC			
According to Central Pathology Review Committee (CPRC), 78.5% of patients had DLBCL, 4.8% had DLBCL with follicular components and 2.6% had FL Grade 3. Other patients were not diagnosed for lymphoma (4.8%), had other lymphoma (3.8%), were not assessed (3.5%) or assessment was missing (1.9%). No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.388).			
Units: Subjects			
DLBCL	120	125	245
DLBCL with follicular components	5	10	15
FL Grade 3	3	5	8
Non-diagnostic for lymphoma	10	5	15
Other lymphoma (none of the above)	8	4	12
Not assessed	6	5	11
Missing	3	3	6
Number of prior lines of therapy for DLBCL or FL Grade 3			
Most patients had received 1 prior therapy (61.9%) for DLBCL or FL Grade 3 lymphoma; 21.8% had received 2 prior therapies and 11.5% received 3 prior therapies. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.823).			
Units: Subjects			
0 prior therapy	9	6	15
1 prior therapy	93	100	193
2 prior therapies	35	33	68
3 prior therapies	18	18	36
IPI Score			
Most patients (53.2%) had a baseline IPI score ≥ 3 . No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.285).			
Units: Subjects			
Score = 0	2		2
Score = 1	24	17	41
Score = 2	47	56	103
Score ≥ 3	82	84	166
Reason for ineligibility for HDC and SCT			
Main reason for non-eligibility for high-dose chemotherapy (HDC) and stem cell transplant (SCT) was "patient is not adequately fit" (39.4%). No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.579).			
Units: Subjects			
Patient is not adequately fit	57	66	123
Patient refused	22	18	40
Prior transplant	16	12	28

Co-morbid conditions	11	15	26
Failure to mobilize adequate number of cells	2		2
Other	47	46	93
ECOG PS			
Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline was 0 for 27.2% of patients, 1 for 51.6% of patients, and 2 for 20.8% of patients; the score was missing for 1 patient (0.3%). No relevant difference was observed between the treatment groups for this baseline characteristic (p = 0.735).			
Units: Subjects			
Score = 0	45	40	85
Score = 1	77	84	161
Score = 2	33	32	65
Missing		1	1
Number of prior systemic therapies			
The treatment groups were comparable in regards to prior NHL therapy. Overall, more than half of the patients (54.8%) received one prior systemic therapy, 24.7% received 2 prior systemic therapies and 17.6% received 3 prior systemic therapies.			
Units: Subjects			
1 therapy	83	88	171
2 therapies	39	38	77
3 therapies	29	26	55
4 therapies	4	5	9
Type of the most recent systemic therapies			
The treatment groups were comparable in regards to prior NHL therapy. For the majority of patients (87.2%) the most recent systemic therapies for NHL prior to inclusion in the study pursued a curative intent.			
Units: Subjects			
Curative	131	141	272
Maintenance	15	8	23
Palliative	5	5	10
Other	4	3	7
Best response to the most recent systemic therapy			
The treatment groups were comparable in regards to prior NHL therapy. The best response to the most recent systemic therapy was complete response (CR) or complete response unconfirmed (CRu) in 55.4% of patients and PR in 30.1%.			
Units: Subjects			
Complete response/complete response unconfirmed	83	90	173
Partial response	49	45	94
Stable disease	10	11	21
Progressive disease	11	9	20
Unknown	2	2	4
Medical history - cardiac history			
Most patients presented with a cardiac history at baseline: 63.9% in the pixantrone + R group and 66.2% in the gemcitabine + R group.			
Units: Subjects			
Patients with any cardiac history events	99	104	203
Patients with no cardiac history events	56	53	109
Body Mass Index (BMI)			
At baseline, the mean BMI was 27.5 kg/m ² ranging from 15 kg/m ² to 62 kg/m ² . No relevant difference between the treatment groups was observed for BMI (p = 0.849).			
Units: kg/m ²			

arithmetic mean	27.5	27.4	
full range (min-max)	15 to 62	16 to 48	-
Time since initial diagnosis of DLBCL or FL Grade 3			
The initial diagnosis of DLBCL or FL Grade 3 was made at a median of 1.9 years (i.e. 22.8 months; ranging from 0 to 15 years) prior to study entry. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.782).			
Units: years			
median	1.8	2.0	
full range (min-max)	0 to 15	0 to 14	-
Time from initiation of first-line therapy for DLBCL or FL Grade 3 until first relapse			
Time from initiation of first-line therapy for DLBCL or FL grade 3 until first relapse was a median of 1.4 years (i.e. 16.8 months). For pixantrone + rituximab, n = 144; for gemcitabine + rituximab, n = 151. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.778).			
Units: years			
median	1.4	1.4	
full range (min-max)	0 to 11	0 to 11	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population was defined as all randomized patients regardless of whether patients received any study treatment, or received a different treatment from the treatment they were randomized to. Patients were analyzed according to the treatment to which they were assigned at randomization.

The ITT population consisted of all 312 patients randomized.

Reporting group values	ITT population		
Number of subjects	312		
Age categorical			
At baseline, most patients were 65 years old or older (78.8% overall). The median age of patients was 73.0 years ranging from 26 to 91 years. Age was well balanced between the treatment groups (p = 0.535).			
Units: Subjects			
Adults (18-64 years)	66		
From 65-84 years	233		
85 years and over	13		
Age continuous			
Units: years			
median	73		
full range (min-max)	26 to 91		
Gender categorical			
At baseline, just over half of the patients were women (56.4%). Gender was well balanced between the treatment groups (p = 0.819).			
Units: Subjects			
Female	176		
Male	136		
Region			
Two thirds of patients (66.7%) were enrolled in Europe and one third (33.3%) in North America. Region was well balanced between the treatment groups.			

Units: Subjects			
North America	104		
Europe	208		
Race			
The large majority (96.8%) of patients were white. Race was well balanced between the treatment groups (p = 0.165).			
Units: Subjects			
White	302		
Black or African American	5		
Asian	2		
Other	2		
Unknown	1		
Histological subtype assessed by local investigators			
The most common histological subtype assessed by local investigators was DLBCL (77.6% of patients), 13.8% of patients had DLBCL transformed from indolent, and 8.7% had follicular lymphoma (FL) Grade 3 lymphoma. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.644).			
Units: Subjects			
DLBCL	242		
DLBCL transformed from indolent	43		
FL Grade 3	27		
Histology assessed by CPRC			
According to Central Pathology Review Committee (CPRC), 78.5% of patients had DLBCL, 4.8% had DLBCL with follicular components and 2.6% had FL Grade 3. Other patients were not diagnosed for lymphoma (4.8%), had other lymphoma (3.8%), were not assessed (3.5%) or assessment was missing (1.9%). No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.388).			
Units: Subjects			
DLBCL	245		
DLBCL with follicular components	15		
FL Grade 3	8		
Non-diagnostic for lymphoma	15		
Other lymphoma (none of the above)	12		
Not assessed	11		
Missing	6		
Number of prior lines of therapy for DLBCL or FL Grade 3			
Most patients had received 1 prior therapy (61.9%) for DLBCL or FL Grade 3 lymphoma; 21.8% had received 2 prior therapies and 11.5% received 3 prior therapies. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.823).			
Units: Subjects			
0 prior therapy	15		
1 prior therapy	193		
2 prior therapies	68		
3 prior therapies	36		
IPI Score			
Most patients (53.2%) had a baseline IPI score ≥ 3 . No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.285).			
Units: Subjects			
Score = 0	2		
Score = 1	41		
Score = 2	103		
Score ≥ 3	166		
Reason for ineligibility for HDC and SCT			

Main reason for non-eligibility for high-dose chemotherapy (HDC) and stem cell transplant (SCT) was "patient is not adequately fit" (39.4%). No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.579).

Units: Subjects			
Patient is not adequately fit	123		
Patient refused	40		
Prior transplant	28		
Co-morbid conditions	26		
Failure to mobilize adequate number of cells	2		
Other	93		

ECOG PS			
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Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline was 0 for 27.2% of patients, 1 for 51.6% of patients, and 2 for 20.8% of patients; the score was missing for 1 patient (0.3%). No relevant difference was observed between the treatment groups for this baseline characteristic (p = 0.735).

Units: Subjects			
Score = 0	85		
Score = 1	161		
Score = 2	65		
Missing	1		

Number of prior systemic therapies			
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The treatment groups were comparable in regards to prior NHL therapy. Overall, more than half of the patients (54.8%) received one prior systemic therapy, 24.7% received 2 prior systemic therapies and 17.6% received 3 prior systemic therapies.

Units: Subjects			
1 therapy	171		
2 therapies	77		
3 therapies	55		
4 therapies	9		

Type of the most recent systemic therapies			
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The treatment groups were comparable in regards to prior NHL therapy. For the majority of patients (87.2%) the most recent systemic therapies for NHL prior to inclusion in the study pursued a curative intent.

Units: Subjects			
Curative	272		
Maintenance	23		
Palliative	10		
Other	7		

Best response to the most recent systemic therapy			
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The treatment groups were comparable in regards to prior NHL therapy. The best response to the most recent systemic therapy was complete response (CR) or complete response unconfirmed (CRu) in 55.4% of patients and PR in 30.1%.

Units: Subjects			
Complete response/complete response unconfirmed	173		
Partial response	94		
Stable disease	21		
Progressive disease	20		
Unknown	4		

Medical history - cardiac history			
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Most patients presented with a cardiac history at baseline: 63.9% in the pixantrone + R group and 66.2% in the gemcitabine + R group.

Units: Subjects			
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Patients with any cardiac history events	203		
Patients with no cardiac history events	109		
Body Mass Index (BMI)			
At baseline, the mean BMI was 27.5 kg/m ² ranging from 15 kg/m ² to 62 kg/m ² . No relevant difference between the treatment groups was observed for BMI (p = 0.849).			
Units: kg/m ²			
arithmetic mean	27.5		
full range (min-max)	15 to 62		
Time since initial diagnosis of DLBCL or FL Grade 3			
The initial diagnosis of DLBCL or FL Grade 3 was made at a median of 1.9 years (i.e. 22.8 months; ranging from 0 to 15 years) prior to study entry. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.782).			
Units: years			
median	1.9		
full range (min-max)	0 to 15		
Time from initiation of first-line therapy for DLBCL or FL Grade 3 until first relapse			
Time from initiation of first-line therapy for DLBCL or FL grade 3 until first relapse was a median of 1.4 years (i.e. 16.8 months). For pixantrone + rituximab, n = 144; for gemcitabine + rituximab, n = 151. No relevant difference between the treatment groups was observed for this baseline disease characteristic (p = 0.778).			
Units: years			
median	1.4		
full range (min-max)	0 to 11		

End points

End points reporting groups

Reporting group title	Pixantrone + Rituximab
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Reporting group description:

Investigational therapy arm: The intent-to-treat (ITT) population included all 155 patients randomized to pixantrone + rituximab (pixantrone + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (153 patients); 2 patients were excluded from the safety population. The safety population was used for all safety analyses.

83 patients in the ITT population discontinued treatment due to: progressive disease (47), adverse event (21), consent withdrawal (6), death (5), or other reason (4).

Reporting group title	Gemcitabine + Rituximab
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Reporting group description:

Control therapy arm: The intent-to-treat (ITT) population included all 157 patients randomized to gemcitabine + rituximab (gemcitabine + R). The ITT population was used for analysis of demographic and baseline characteristics and efficacy. The safety population included all randomized patients who received at least one administration of study drug (149 patients); 8 patients were excluded from the safety population. The safety population was used for all safety analyses.

96 patients discontinued treatment due to: progressive disease (50), adverse event (15), consent withdrawal (16), death (10), or other reason (5).

Subject analysis set title	ITT population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The intent-to-treat (ITT) population was defined as all randomized patients regardless of whether patients received any study treatment, or received a different treatment from the treatment they were randomized to. Patients were analyzed according to the treatment to which they were assigned at randomization.

The ITT population consisted of all 312 patients randomized.

Primary: Progression-free Survival (PFS) per IRC assessment in the ITT population

End point title	Progression-free Survival (PFS) per IRC assessment in the ITT population
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End point description:

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from the date of randomization to the date of progressive disease (PD) or death due to any cause (whichever occurred first). The primary analysis of PFS was based on disease progression as determined by the Independent Radiology Committee (IRC).

Median PFS and the corresponding 95% CI were estimated using the Kaplan-Meier method and were presented by treatment arm. The Kaplan-Meier curve was plotted.

End point type	Primary
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End point timeframe:

Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6 months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up, intermediate follow-up, & survival follow-up periods.

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Months				
median (confidence interval 95%)	7.3 (5.2 to 8.4)	6.3 (4.4 to 8.1)		

Attachments (see zip file)	Kaplan-Meier Curve of PFS in ITT/Study PIX306_Figure_KM
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Statistical analyses

Statistical analysis title	Treatment difference in PFS
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Statistical analysis description:

PFS was compared between the 2 treatment arms in the ITT population using a stratified log-rank test adjusted for randomization stratification factors (number of prior therapies/International Prognostic Index [IPI]/time from start of 1st line therapy to 1st relapse). The adjusted hazard ratio and 95% CI were calculated using the Cox proportional hazards model adjusted for randomization stratification factors.

Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2782
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.14

Secondary: Overall Survival (OS) in the ITT Population (Interim Results)

End point title	Overall Survival (OS) in the ITT Population (Interim Results)
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End point description:

Overall survival (OS) was defined as the time from the date of randomization to the date of death due to any cause. If a patient was alive or the survival status was unknown by the data cut-off date for analysis, survival was censored at the last date the patient was known to be alive. The following analysis of OS is the first interim analysis planned by the protocol, which was carried out at the time of the core database lock.

At the time of the first interim analysis, 177 deaths had occurred: 94 (60.6%) in the pixantrone + R group and 83 (52.9%) in the gemcitabine + R group.

Median OS and the corresponding 95% CI were estimated using the Kaplan-Meier method and were presented by treatment arm. The Kaplan-Meier curve was plotted.

End point type	Secondary
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End point timeframe:

Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6 months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up, intermediate follow-up, & survival follow-up periods.

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Months				
median (confidence interval 95%)	13.3 (10.1 to 19.8)	19.6 (12.4 to 31.9)		

Attachments (see zip file)	Kaplan-Meier Curve of OS in ITT/Study PIX306_Figure_KM
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Statistical analyses

Statistical analysis title	Treatment difference in OS
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Statistical analysis description:

OS was compared between the 2 treatment arms in the ITT population using a stratified log-rank test adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse). The adjusted hazard ratio and 95% CI were calculated using the Cox proportional hazards model adjusted for randomization stratification factors.

Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4326
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.53

Secondary: Overall Response Rate (ORR) per IRC assessment in the ITT Population

End point title	Overall Response Rate (ORR) per IRC assessment in the ITT Population
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End point description:

The Overall Response Rate (ORR) was defined as the proportion of patients who achieved a Complete Response (CR) or Partial Response (PR) without additional anticancer therapy. Patients who discontinued before any response was observed or received additional anticancer therapy before a response, were considered non-responders.

The 95% CI for ORR in each treatment arm was calculated using the Clopper-Pearson method.

End point type	Secondary
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End point timeframe:

Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6 months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up,

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Percent				
number (confidence interval 95%)	61.9 (53.8 to 69.6)	43.9 (36.0 to 52.1)		

Statistical analyses

Statistical analysis title	Treatment difference in ORR estimate
Statistical analysis description:	
ORR was compared between the 2 treatment arms in the ITT population using the Cochran-Mantel-Haenszel test, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse). The 95% CI for the difference in ORR between the 2 treatment arms was based on the Agresti-Caffo method.	
Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference in ORR estimate
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	28.6

Secondary: Complete Response (CR) per IRC assessment in the ITT population

End point title	Complete Response (CR) per IRC assessment in the ITT population
End point description:	
The Complete Response (CR) rate was defined as the proportion of patients who achieved a CR without additional therapy. Patients who discontinued or received additional anticancer therapy before any response had been observed were considered non-responders.	
The 95% CI for CR in each treatment arm was calculated using the Clopper-Pearson method.	
End point type	Secondary
End point timeframe:	
Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6 months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up, intermediate follow-up, & survival follow-up periods.	

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Percent				
number (confidence interval 95%)	35.5 (28.0 to 43.6)	21.7 (15.5 to 28.9)		

Statistical analyses

Statistical analysis title	Treatment difference in CR estimate
Statistical analysis description:	
CR was compared between the 2 treatment arms in the ITT population using the Cochran-Mantel-Haenszel test, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse). The 95% CI for the difference in CR between the 2 treatment arms was based on the Agresti-Caffo method.	
Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference in CR estimate
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	23.5

Other pre-specified: Duration of Overall Response (DOR) per IRC assessment in the ITT population

End point title	Duration of Overall Response (DOR) per IRC assessment in the ITT population
End point description:	
Duration of Overall Response (DOR) was only defined for CR or PR responders. DOR was calculated as the time from the date of the first documented CR or PR to the date of first documented evidence of PD (or relapse for patients who experienced a CR on this study) or death from any cause.	
Median DOR and the corresponding 95% CI were estimated using the Kaplan-Meier method and were presented by treatment arm.	
End point type	Other pre-specified
End point timeframe:	
Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6 months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up, intermediate follow-up, & survival follow-up periods.	

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Months				
median (confidence interval 95%)	10.0 (6.6 to 17.3)	9.1 (6.5 to 18.5)		

Statistical analyses

Statistical analysis title	Treatment difference in DOR
Statistical analysis description:	
DOR was compared between the 2 treatment arms in the ITT population using an unstratified log-rank test. The estimated hazard ratio and 95% CI were calculated using the Cox proportional hazard model adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse).	
Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8563
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.47

Other pre-specified: Duration of Complete Response (DCR) per IRC assessment in the ITT population

End point title	Duration of Complete Response (DCR) per IRC assessment in the ITT population
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End point description:

Duration of Complete Response (DCR) was defined as the time from the date of the first documented CR to the first documented tumor relapse or death due to any cause.

Median DCR and the corresponding 95% CI were estimated using the Kaplan-Meier method and were presented by treatment arm.

Kaplan-Meier estimate of median DCR, months [95% CI]:

Pixantrone + R: 13.0 [7.1, 30.7]

Gemcitabine + R: 15.4 [7.5, non-estimable]

End point type	Other pre-specified
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End point timeframe:

Disease was assessed at baseline and during treatment (up to six 28-day cycles), early follow-up (6

months), & intermediate follow-up (18 months) periods. Survival was assessed during early follow-up, intermediate follow-up, & survival follow-up period.

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Months				
number (confidence interval 95%)	13.0 (7.1 to 30.7)	15.4 (7.5 to 9999.9)		

Statistical analyses

Statistical analysis title	Treatment difference in DCR
Statistical analysis description:	
DCR was compared between the 2 treatment arms in the ITT population using a log-rank test. The estimated hazard ratio and 95% CI were calculated using the Cox proportional hazards model adjusted for randomization stratification factors.	
Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9374
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.88

Other pre-specified: Patients who received Stem Cell Transplant (SCT) after start of study treatment in the ITT population

End point title	Patients who received Stem Cell Transplant (SCT) after start of study treatment in the ITT population
End point description:	
The proportion of patients who received a stem cell transplant (SCT) was defined as the percentage of all randomized patients in the ITT population who received a SCT after start of study treatment.	
The 95% CI for SCT in each treatment arm was calculated using the Clopper-Pearson method.	
End point type	Other pre-specified
End point timeframe:	
After start of study treatment and through the treatment period (up to six 28-day cycles), early follow-up (6 months) period, intermediate follow-up (18 months) period, and survival follow-up period.	

End point values	Pixantrone + Rituximab	Gemcitabine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: percent				
number (confidence interval 95%)	2.6 (0.7 to 6.5)	1.3 (0.2 to 4.5)		

Statistical analyses

Statistical analysis title	Treatment difference in SCT estimate
Statistical analysis description:	
SCT was compared between the 2 treatment arms in the ITT population using the Cochran-Mantel-Haenszel test, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse). The 95% CI for the difference in SCT between the 2 treatment arms was based on the Agresti-Caffo method.	
Comparison groups	Pixantrone + Rituximab v Gemcitabine + Rituximab
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4015
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference in SCT estimate
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	4.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For randomized patients, from signing of informed consent. For nonrandomized screen failures, SAEs from signing of informed consent to time of screen failure.

Adverse event reporting additional description:

Adverse events could have been spontaneously reported or elicited during open-ended questioning, examination or evaluation of the patient.

Subjects who experienced multiple events within the same preferred term (PT) were counted once per PT at the highest severity grade.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Pixantrone + Rituximab
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Reporting group description:

Treatment -emergent adverse events (TEAEs) for patients who received pixantrone + R are reported.

Serious TEAEs that occurred in 2 or more patients in either treatment arm and all serious TEAEs leading to death are reported.

Non-serious TEAEs that occurred in 10% or more of patients in either treatment arm are reported.

Reporting group title	Gemcitabine + Rituximab
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Reporting group description:

Treatment -emergent adverse events (TEAEs) for patients who received gemcitabine + R are reported.

Serious TEAEs that occurred in 2 or more patients in either treatment arm and all serious TEAEs leading to death are reported.

Non-serious TEAEs that occurred in 10% or more of patients in either treatment arm are reported.

Serious adverse events	Pixantrone + Rituximab	Gemcitabine + Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 153 (38.56%)	57 / 149 (38.26%)	
number of deaths (all causes)	93	81	
number of deaths resulting from adverse events	14	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	3 / 153 (1.96%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Disseminated large cell lymphoma	Additional description: This serious TEAE occurred in 1 patient in the pixantrone + R arm and it led to death.		

subjects affected / exposed	1 / 153 (0.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	3 / 153 (1.96%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrial fibrillation			
subjects affected / exposed	2 / 153 (1.31%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cytotoxic cardiomyopathy			
subjects affected / exposed	2 / 153 (1.31%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 153 (1.31%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 153 (0.00%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	2 / 3	
Cardiac failure congestive			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 153 (1.96%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	5 / 153 (3.27%)	8 / 149 (5.37%)	
occurrences causally related to treatment / all	5 / 5	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 153 (3.27%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 153 (1.31%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 153 (2.61%)	8 / 149 (5.37%)	
occurrences causally related to treatment / all	1 / 4	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 153 (1.31%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	2 / 153 (1.31%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized oedema			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: This serious TEAE occurred in 1 patient in each treatment arm. This serious TEAE in the pixantrone + R arm led to death.		
subjects affected / exposed	1 / 153 (0.65%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	

Multi-organ failure		Additional description: This serious TEAE occurred in 1 patient in the pixantrone + R arm and it led to death.	
subjects affected / exposed	1 / 153 (0.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 153 (0.65%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 153 (1.31%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 153 (1.31%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 153 (0.65%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration		Additional description: This serious TEAE occurred in 1 patient in the gemcitabine + R arm and it led to death.	
subjects affected / exposed	0 / 153 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	2 / 153 (1.31%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 153 (1.31%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hydronephrosis			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic	Additional description: This serious TEAE occurred in 1 patient in the pixantrone + R arm and it led to death. This patient also experienced cerebrovascular accident (serious TEAE, related to treatment, fatal).		
subjects affected / exposed	1 / 153 (0.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 153 (5.23%)	4 / 149 (2.68%)	
occurrences causally related to treatment / all	3 / 8	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	2 / 153 (1.31%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	2 / 153 (1.31%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 153 (1.31%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 153 (0.65%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 153 (0.00%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 153 (0.00%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 153 (1.31%)	3 / 149 (2.01%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis	Additional description: This serious TEAE occurred in 1 patient in the pixantrone + R arm and it led to death.		
subjects affected / exposed	1 / 153 (0.65%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pixantrone + Rituximab	Gemcitabine + Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 153 (97.39%)	146 / 149 (97.99%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	17 / 153 (11.11%)	6 / 149 (4.03%)	
occurrences (all)	17	6	

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	106 / 153 (69.28%)	88 / 149 (59.06%)	
occurrences (all)	106	88	
Anaemia			
subjects affected / exposed	42 / 153 (27.45%)	74 / 149 (49.66%)	
occurrences (all)	42	74	
Thrombocytopenia			
subjects affected / exposed	25 / 153 (16.34%)	98 / 149 (65.77%)	
occurrences (all)	25	98	
Leukopenia			
subjects affected / exposed	12 / 153 (7.84%)	19 / 149 (12.75%)	
occurrences (all)	12	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	45 / 153 (29.41%)	34 / 149 (22.82%)	
occurrences (all)	45	34	
Pyrexia			
subjects affected / exposed	21 / 153 (13.73%)	35 / 149 (23.49%)	
occurrences (all)	21	35	
Asthenia			
subjects affected / exposed	20 / 153 (13.07%)	18 / 149 (12.08%)	
occurrences (all)	20	18	
Oedema peripheral			
subjects affected / exposed	19 / 153 (12.42%)	31 / 149 (20.81%)	
occurrences (all)	19	31	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	38 / 153 (24.84%)	24 / 149 (16.11%)	
occurrences (all)	38	24	
Constipation			
subjects affected / exposed	35 / 153 (22.88%)	20 / 149 (13.42%)	
occurrences (all)	35	20	
Diarrhoea			
subjects affected / exposed	24 / 153 (15.69%)	20 / 149 (13.42%)	
occurrences (all)	24	20	

Vomiting subjects affected / exposed occurrences (all)	21 / 153 (13.73%) 21	17 / 149 (11.41%) 17	
Stomatitis subjects affected / exposed occurrences (all)	16 / 153 (10.46%) 16	10 / 149 (6.71%) 10	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	19 / 153 (12.42%) 19	13 / 149 (8.72%) 13	
Cough subjects affected / exposed occurrences (all)	19 / 153 (12.42%) 19	19 / 149 (12.75%) 19	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	29 / 153 (18.95%) 29	2 / 149 (1.34%) 2	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	28 / 153 (18.30%) 28	15 / 149 (10.07%) 15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2010	Protocol Amendment 1 concerned the clarification of PFS definition and the modification of censoring rules. For patients "who received any new lymphoma-directed therapy (other than rituximab as maintenance) before progression of disease", the date of censoring was defined as the date of the "last radiologic assessment prior to the start of the new therapy", instead of the "date of first administration of additional treatment".
10 March 2011	<p>Protocol Amendment 2 concerned mainly:</p> <ul style="list-style-type: none">- The change in the study primary objective: OS, initially a secondary objective, was added to PFS as a combined primary objective. Statistical methods including sample size determination were updated taking into account this modification.- The increase in the number of patients to be randomized (from 300 to 350).- The replacement of the stratification factor "prior SCT" by "length of time from initiation of first-line therapy for aggressive NHL until first relapse".- The addition of safety criteria (study-related AEs and some cardiac events and assessments) during the Follow-up periods.- As regards to the reporting of AEs, it was also specified that cardiac AEs \geq grade 3 were to be collected until the end of the study and followed until resolution or no further improvement was expected.- Specifications on clinical examination were added.- The modification of inclusion criteria (bone core biopsy was to be obtained within 8 weeks prior to randomization, addition of the necessity to confirm the response to CHOP-R by a second radiographic assessment; removal of the 24-week delay between day 1 of last cycle of CHOP-R or equivalent treatment and subsequent relapse, and update of the laboratory requirements for platelets and absolute neutrophil count).- The addition of primary refractory aggressive NHL as an exclusion criterion.- An update of pixantrone and gemcitabine dose adjustments and delays for hematologic toxicity.- Specifications for low-dose corticosteroids use as concomitant medication.- For the selection of target lesions, measurable lesions in a previously radiated site could not be considered target lesions.- Wording specifications.- Procedures specifications.

03 August 2011	<p>Protocol Amendment 3 included:</p> <ul style="list-style-type: none"> - An update of Safety information in the background section. - The clarification of the use of the terms "NHL" and "DLBCL". - The modification of inclusion criteria: bone marrow biopsy criteria were clarified, prior CHOP-R was allowed for any type of NHL, patients with transformed follicular lymphoma who may not have received CHOP-R as first-line therapy for aggressive NHL could also be included in the study, definition of measurable disease was adjusted to be consistent with other Sections in the protocol, and it was specified that DLBCL diagnosis was to be confirmed by pathologic review. - The modification of exclusion criteria: definitions of measurable disease and primary refractory disease were updated and clarified, CNS involvement was further detailed, and enrolment of patients who had had certain low-risk cancers commonly found in this population was finally allowed. - Disease Assessment Criteria were extensively clarified. - PET scan requirements were modified. - The prior requirement for central evaluation of echocardiograms was removed, since implementing the central read processes negatively impacted timely site initiation and accrual of patients. There was no clear need for a retrospective central read, but there was considerable negative impact; therefore, central read was deleted. Local echo evaluations were used for safety and treatment decisions. - The timing of IDMC meetings was clarified. - A recommendation was added that rituximab be administered first, and the section regarding drugs administration was reorganized to allow investigators more clearly identifying potential rituximab-related adverse reactions. The window for pixantrone administration was clarified. - The requirement for physical examinations before study drug administration was clarified. - Procedures for dose adjustments and delays were detailed. - Safety reporting was clarified and revised. - Pathology procedures were clarified.
05 January 2012	<p>Protocol Amendment 4 aimed to:</p> <ul style="list-style-type: none"> - Change the primary endpoint of the study to "overall survival" only, following FDA recommendations. PFS was therefore a secondary objective. All the protocol (primary and secondary endpoints, statistical analyses, etc) was modified accordingly. - An interim analysis of OS, to be done when 150 deaths (50%) had occurred, was planned. The final OS analysis was to be performed when 300 deaths had occurred. - Stratification factors were adjusted. - Criteria for eligible patients were modified and clarified to ensure safety and enrolment of the target population. - Bone marrow biopsy requirements were revised. - Troponin sample requirements and processing were clarified. - Dose adjustments and delays for toxicity were detailed. - Follow-up for randomized patients versus not randomized patients was clarified. - The definition of measurable disease was slightly revised. - PET scan requirements were clarified.
09 April 2012	<p>Protocol Amendment 5, for North America (NA), concerned:</p> <ul style="list-style-type: none"> - For the primary objective, eligibility of patients was further detailed: patients were to "have no progression for at least 12 weeks after last dose of a treatment regimen" instead of "were to have had a response to prior therapy". - In response to a recommendation from the EMA, pixantrone dose was expressed in its base form (instead of its salt form) in the whole document. - It was specified that the study would be conducted in the United States, Canada, Eastern and Western Europe and South America. - Requirements for entering Survival Follow-up period were updated. - The formula to calculate doxorubicin equivalent dose was replaced. - Wording specifications. - Procedures specifications.

18 June 2012	<p>Protocol Amendment 5 NNA, for Non-North America (NNA), included:</p> <ul style="list-style-type: none"> - The rationale for rituximab-pixantrone combination was further detailed (NA + NNA). - It was specified that the study would be conducted in NA, Western Europe and potentially Eastern Europe (NNA). - It was specified that the study would be conducted in NA, Western Europe and Eastern Europe for (NA). - Inclusion criterion on contraceptive methods to be used was updated (NA + NNA). - Possible adverse reactions associated with rituximab were added and concerned cytokine release syndrome, hypersensitivity reactions and anaphylaxis and progressive multifocal leukoencephalopathy (NA + NNA). - Recommendations were given on the use of some concomitant medications (especially those metabolized by CYP1A2) when co-administered with pixantrone (NA + NNA). - In response to EMA, the pixantrone dose was expressed in its base form (instead of its salt form) in the whole document (NA).
31 August 2012	<p>Protocol Amendment 6, for North America (NA) included:</p> <ul style="list-style-type: none"> - The rationale for rituximab-pixantrone combination was further detailed (NA + NNA). - It was specified that the study would be conducted in NA, Western Europe and potentially Eastern Europe (NNA). - It was specified that the study would be conducted in NA, Western Europe and Eastern Europe for (NA). - Inclusion criterion on contraceptive methods to be used was updated (NA + NNA). - Possible adverse reactions associated with rituximab were added and concerned cytokine release syndrome, hypersensitivity reactions and anaphylaxis and progressive multifocal leukoencephalopathy (NA + NNA). - Recommendations were given on the use of some concomitant medications (especially those metabolized by CYP1A2) when co-administered with pixantrone (NA + NNA). - In response to EMA, the pixantrone dose was expressed in its base form (instead of its salt form) in the whole document (NA).
17 October 2012	<p>Protocol Amendment 6 NNA, for Non-North America (NNA), concerned mainly:</p> <ul style="list-style-type: none"> - In response to EMA, the pixantrone dose was expressed in its base form (instead of its salt form) in the whole document. - It was specified that the study would be conducted in NA, Eastern and Western Europe. - Procedures for reporting AEs updated.
16 September 2013	<p>Protocol Amendment 7 NNA, for Non-North America (NNA), and aimed to:</p> <ul style="list-style-type: none"> - Entirely revise the synopsis consistently with the protocol body: several sections were added (No. of study, Name of sponsor, Phase of development, Investigational Drug, Duration of Study and Treatment, Planned No. of Patients, Test Product and Reference therapy, Treatment regimen, Inclusion and Exclusion criteria, Schedule of treatment and assessments, Criteria for evaluation (renamed section title)). - Change in EOT window: The EOT visit was to occur at 4 to 7 weeks after last study drug dose, inclusive, or before non-protocol NHL therapy was given, whichever occurred first instead of "the EOT visit occurs at 5 weeks \pm 1week after the last study drug administration or before non-protocol NHL therapy is given". - Gemcitabine dose modifications for hematologic toxicity were completed. - Gemcitabine and pixantrone dose modifications for non-hematologic toxicity were completed. - Concomitant medications were updated: additional recommendations for drug's photosensitivity. - Use of local laboratories for urgent clinical decisions: Local labs were required, as needed, for time-limited evaluation windows, per protocol, and to support urgent clinical decisions. - Details were added for the description of visits schedules and assessments (for the screening period, the End of treatment visit, and Follow-up periods). - The description of disease assessment was also modified (in case no EOT PET scan could be obtained, for bone marrow biopsy...). - Specification on AEs and AEs reporting were added. - Some minor revisions and wording specifications were implemented.

25 July 2014	<p>Protocol Amendment 8, for NA and NNA, unified previous NA and NAA versions. Major changes were:</p> <ul style="list-style-type: none"> - Primary endpoint (previously OS) was replaced by PFS. - Number of subjects to be randomized was decreased from 350 to 260 patients. Enrolment was to be continued until 195 PFS events occurred, or approximately 260 patients were enrolled, whichever occurred first. Enrolment period was planned approximately 60 months from study initiation. - It was specified that no interim analysis of PFS was planned. - Added exploratory objectives (assessment of DOR and DCR between treatments, proportion of patients who received a SCT after study treatment). - Rituximab given as maintenance therapy was not allowed prior to the EOT visit per protocol window. - Added precisions for patients entering Follow-up periods. - Added definition of EOS (i.e. date when the required OS events have occurred or the study is terminated). - Criteria for efficacy evaluation were further detailed. - Consequently to the change in the objectives and primary criteria, statistical methods were adapted, including the sample size re-estimation. - Updated pixantrone safety in clinical study in the background and rationale. - Precisions were given for patients still on treatment at the end of recruitment (to continue per protocol until EOT and enter the survival follow-up or directly to enter the survival follow-up period). - Added details for completion and discontinuation of treatment. - Added information about pixantrone handling, preparation, administration and storage. - Added recommendations for drug's for drug's photosensitivity. - Visit schedule and assessments as well as imaging ad criteria for response, were further detailed. - Updated definition and reporting of AEs. - Added length of time from initiation of therapy for DLBCL or FL grade 3 until first relapse to subgroup analyses. - Added informed consent for collecting survival information. - Added PK study.
10 July 2017	<p>Protocol Amendment 9 aimed to:</p> <ul style="list-style-type: none"> - Updated the total number of patients to be enrolled, after simulation performed by the sponsor, from 260 to 320 patients, to reach the 195 PFS events (per IRC) within a reasonable timeline to meet the study report due date. - Increased enrolment period from 60 to 80 months, to accommodate the increase in the number of planned patients' enrolment. - Added one additional interim analysis for secondary efficacy endpoint OS, i.e. when 190 OS events (86% of the required number of OS events) have occurred, due to much slower occurrence of OS events than expected. Indeed, based on the updated projection, the time to achieve 220 OS events is year 2022, more than 3 years from the first interim analysis. Adding the 2nd OS interim analysis would provide a chance to stop the trial earlier if the treatment demonstrated superior survival benefit. - The hierarchy order for testing the secondary efficacy endpoints was updated. In view of the importance of OS in these patients and in order to better match the study objectives, there was reorganization of the order of endpoints testing, to put OS ahead of overall response and CR, in the hypothesis testing hierarchy of secondary endpoints. - Clarified treatment blinding. - Added a sub-group analysis. As the current indication is in 3rd and 4th line, a subgroup analysis defined by 0-1 line versus more than 2 lines was added to confirm the efficacy and safety of pixantrone in the current indication and to evaluate them in 2nd line.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Following the analysis of the primary endpoint of this study, it was decided by the Sponsor not to continue the study until the target 220 events for the OS analysis, but terminate it within 6 months of the data cut-off date (14 Sep 2018).

Notes: